Electrocardiographic Predictors of Arrhythmic Death and Total Mortality in the Multicenter Unsustained Tachycardia Trial

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Background—Stratifiers of sudden and total mortality risk are needed to optimally target preventive therapies in patients with coronary artery disease and impaired ventricular function. We assessed the prognostic significance of ECG markers of conduction abnormalities and left ventricular hypertrophy in the Multicenter Unsustained Tachycardia Trial (MUSTT).

Methods and Results—We analyzed the ECGs of 1638 patients from MUSTT who did not receive antiarrhythmic therapy (antiarrhythmic medication or implantable cardioverter-defibrillator). After adjustment for other significant factors, left bundle-branch block and intraventricular conduction delay were associated with a 50% increase in the risk of both arrhythmic and total mortality. Right bundle-branch block was not associated with arrhythmic or total mortality. Left ventricular hypertrophy was the only ECG predictor of arrhythmic (hazard ratio, 1.35; 95% CI, 1.08 to 1.69) but not total mortality.

Conclusions—in patients with coronary artery disease, depressed left ventricular function, and nonsustained ventricular tachycardia, QRS prolongation resulting from left bundle-branch block or intraventricular conduction delay but not right bundle-branch block provided prognostic information about the risk of arrhythmic and total mortality independently of electrophysiological evaluation and ejection fraction. Left ventricular hypertrophy was associated with increased arrhythmic but not total mortality. (Circulation. 2004;110:766-769.)

Key Words: bundle-branch block: death, sudden: hypertrophy: trials

As the potential population for prophylactic implantable cardioverter-defibrillator (ICD) implantation continues to grow, so does the need to develop specific markers to identify those patients at greatest risk for arrhythmias best treated by implanted devices. Left ventricular hypertrophy (LVH) and abnormalities of electrical conduction have been associated with risk of sudden cardiac death. This association is stronger in the presence of left ventricular dysfunction. Recent data suggesting QRS prolongation to be an important stratifier of risk necessitate further characterization of conduction abnormalities to identify populations at greatest risk of death. In this analysis, we analyzed the relation between ECG abnormalities and occurrence of arrhythmic and total mortality in the Multicenter Unsustained Tachycardia Trial (MUSTT).

Methods

Patients

MUSTT was a randomized, controlled trial designed to determine whether electrophysiologically guided antiarrhythmic therapy would reduce arrhythmic and total mortality in patients with documented coronary artery disease, nonsustained ventricular tachycardia, and depressed (ejection fraction ≤40%) left ventricular function. The details of patient enrollment and the protocol of MUSTT have already been described. In brief, all patients underwent a screening electrophysiology study. Patients who had a sustained ventricular arrhythmia induced during the electrophysiology study that met specified criteria for randomization were randomized to electrophysiology-guided antiarrhythmic therapy or to no specific antiarrhythmic therapy (standard medical therapy, including β-adrenergic blocking agents and ACE inhibitors). Ventricular tachyarrhythmias that met the criteria for randomization included sustained monomorphic ventricular tachycardia induced by 1 to 3 extrastimuli or burst pacing and sustained polymorphic ventricular tachycardia induced by 1 or 2 extrastimuli. Those patients who did not have an arrhythmia that met criteria for randomization were followed up in a registry. The population (n=1638) included in this analysis consisted of patients who did not receive treatment (antiarrhythmic drug or ICD) in both the registry (n=1316) and randomized (n=322) populations. Patients who received an antiarrhythmic drug before discharge from the hospital or an ICD within 90 days of enrollment were excluded from analysis. Standard 12-lead ECGs.
were collected from all patients at the time of enrollment in the absence of antiarrhythmic drug therapy. All ECGs were analyzed in a blinded fashion by 2 readers as part of a centralized core laboratory (M.E.J., A.E.B., J.D.F., R.L.P., W.B., M.F.O.).

### End Points

The primary end point of the study was cardiac arrest or arrhythmic death. Secondary end points consisted of cardiac death and total mortality. A modified Hinkle-Thaler system was used to classify deaths.7 Arrhythmic deaths were defined as unwitnessed deaths in patients known to be stable within 24 hours of the event, witnessed sudden (instantaneous) deaths, nonsudden deaths resulting from toxic effects of antiarrhythmic medications, and deaths caused by complications from implanted defibrillators. Cardiac arrest was defined as the sudden loss of consciousness requiring DC countershock to restore consciousness or hemodynamic stability. Events were classified by an events committee blinded to inducibility and treatment status, as previously reported.6

### Definitions

Intraventricular conduction delay (IVCD) was defined as QRS duration ≥0.11 seconds, but morphology differs from left bundle-branch block (LBBB) or right bundle-branch block (RBBB). LBBB was defined as QRS duration ≥0.12 seconds; delayed onset of intrinsicoid deflection in V1, V5, and V6 >0.05 seconds; broad monophasic, usually notched R waves in V1, V5, and V6; and Rs or QS complexes in right precordial leads. RBBB was defined as QRS duration ≥0.12 seconds; rsR', rSR', or qR (with terminal delay) complexes in V1, rsR' or rSR' complexes in V2; delayed onset of intrinsicoid deflection in V1 and V5 >0.05 seconds; wide, slurred S wave in V1, V5, and V6; and normal or slightly prolonged QRS duration (0.06 to 0.08 seconds) of QRS. Left anterior hemiblock was defined as left-axis deviation with frontal QRS axis between −30° and −90°; qR complex or an R wave in V1 and aVL, rS complex in V5; normal or slightly prolonged QRS duration (0.08 to 0.10 seconds); and no other entities responsible for left-axis deviation. LVH was defined as an R wave in V1 plus S wave in lead V5 >25 mm, R wave in aVL ≥11 mm, or R wave in V1 or V5 >25 mm; R wave in V1 or V5 plus S wave in V5 >35 mm; and onset of intrinsicoid deflection in V1 or V5 ≥0.05 second.

### Statistical Analysis

The distributions of baseline characteristics are summarized with medians and 25th and 75th percentiles for continuous variables and percentages for categorical variables. Group differences in baseline characteristics were assessed with the Wilcoxon rank-sum test (for continuous variables) and the \( \chi^2 \) test (for categorical variables). All tests of significance were 2 tailed. Covariate-adjusted analyses of the effects of baseline ECG characteristics on the outcomes of (1) arrhythmic death and cardiac arrest and (2) total mortality were performed with the Cox proportional-hazards model.6,8 Covariates included in these analyses were electrophysiological inducibility, age, ejection fraction, recent angina, prior CABG, prior angioplasty, race, congestive heart failure, NYHA classification, medications (aspirin, digoxin, \( \beta \)-blocker, ACE inhibitor) at hospital discharge and the number of vessels with ≥75% stenosis. Hazard ratios (HRs) and 95% CIs were calculated with the Cox model.

### Results

LVH was present in 46% of patients, IVCD in 17%, LBBB in 38%, RBBB in 8%, LBBB in 5%, left anterior hemiblock in 12%, and atrial fibrillation in 8% of patients. Patients with LVH were slightly older with lower ejection fractions and had more congestive heart failure than those without LVH (Table 1). Patients with LVH also had fewer myocardial infarctions and less induced sustained ventricular tachycardia compared with those without LVH. Patients with LVH or IVCD were slightly older and had more remote myocardial infarctions, fewer prior angioplasties, lower ejection fractions, and a greater incidence of congestive heart failure than those without LBBB or IVCD (Table 2). The percent of patients having inducible sustained ventricular tachycardia was similar in patients with and without LBBB or IVCD (36% versus 34%, respectively).

### Left Ventricular Hypertrophy

LVH was a significant predictor of arrhythmic but not total mortality in multivariable analysis controlled for multiple
factors, including induction of ventricular arrhythmia (HR, 1.35; 95% CI, 1.08 to 1.69; Table 3).

Left-Axis Deviation
Left anterior hemiblock was associated with total (HR, 1.25; 95% CI, 1.00 to 1.55) but not arrhythmic (Table 3) mortality.

IVCD and BBB
In multivariable analysis, nonspecific intraventricular conduction delay was a significant predictor of both arrhythmic (HR, 1.44; 95% CI, 1.11 to 1.88) and total (HR, 1.47; 95% CI, 1.22 to 1.78) mortality. The presence of LBBB was significantly associated with arrhythmic (HR, 1.49; 95% CI, 1.02 to 2.17) and total (HR, 1.61; 95% CI, 1.26 to 2.08) mortality. Note that for both nonspecific IVCD and LBBB, the HRs for arrhythmic death are similar to the HRs for total mortality. RBBB was not a predictor of arrhythmic or total mortality (Table 3).

## Discussion
In this study, IVCD, LBBB, and atrial fibrillation all predicted both arrhythmic death and total mortality. LVH was the only ECG finding that predicted arrhythmic death independently of total mortality. The predictive value of all of these findings proved to be independent of the results of invasive electrophysiology study and other baseline factors associated with outcome.

## Left Ventricular Hypertrophy
ECG evidence of LVH was associated with a 35% increase in the risk of arrhythmic death regardless of the results of electrophysiology study. Nearly 50% of the population in this analysis had LVH. This large prevalence is expected in patients with coronary artery disease and left ventricular dysfunction.1 The untreated group with LVH in MUSTT had more severe left ventricular dysfunction but fewer myocardial infarctions than those without LVH. This suggests that LVH may be associated with the myopathic process in many patients with coronary artery disease. The lower rate of induced ventricular tachycardia in patients with LVH may be related to fewer myocardial infarctions (substrate for reentrant arrhythmias). Proarrhythmia related to LVH may occur through the development of nonreentrant arrhythmias secondary to early afterdepolarizations.2 Our findings are consistent with previous studies demonstrating an association between

<table>
<thead>
<tr>
<th>TABLE 3. Adjusted Cox Models*</th>
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<tbody>
<tr>
<td>Adjusted for Baseline Factors*</td>
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</table>

<table>
<thead>
<tr>
<th>Arhythmic death or cardiac arrest</th>
<th>Wald $\chi^2$</th>
<th>$P$</th>
<th>HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>IVCD</td>
<td>7.29</td>
<td>0.0069</td>
<td>1.44</td>
<td>(1.11, 1.88)</td>
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<td>LBBB</td>
<td>4.22</td>
<td>0.0400</td>
<td>1.49</td>
<td>(1.02, 2.17)</td>
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<td>LAH</td>
<td>0.10</td>
<td>0.7492</td>
<td>0.95</td>
<td>(0.68, 1.32)</td>
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<tr>
<td>LVH</td>
<td>7.00</td>
<td>0.0082</td>
<td>1.35</td>
<td>(1.08, 1.69)</td>
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<tr>
<td>RBBB</td>
<td>0.04</td>
<td>0.8383</td>
<td>1.05</td>
<td>(0.65, 1.71)</td>
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<tr>
<td>Total mortality</td>
<td>15.65</td>
<td>&lt;0.0001</td>
<td>1.47</td>
<td>(1.22, 1.78)</td>
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<tr>
<td>IVCD</td>
<td>13.94</td>
<td>0.0002</td>
<td>1.61</td>
<td>(1.26, 2.08)</td>
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<tr>
<td>LBBB</td>
<td>3.93</td>
<td>0.0474</td>
<td>1.25</td>
<td>(1.00, 1.55)</td>
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<tr>
<td>LAH</td>
<td>2.49</td>
<td>0.1146</td>
<td>1.14</td>
<td>(0.97, 1.33)</td>
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<tr>
<td>LVH</td>
<td>0.15</td>
<td>0.6953</td>
<td>1.07</td>
<td>(0.77, 1.48)</td>
</tr>
</tbody>
</table>

Lah indicates left anterior hemiblock.

*Adjusted for electrophysiological inducibility, age, ejection fraction, recent angina, prior CABG, prior angioplasty, race, congestive heart failure, NYHA classification, medications (aspirin, digoxin, $\beta$-blocker, ACE inhibitor) at hospital discharge, and number of vessels with $\geq$75% stenosis.
ECG evidence of LVH in patients without structural heart disease and risk of sudden death.\textsuperscript{10}

**Conduction Delay and Prognosis**

In MUSTT, patients with LBBB or IVCD had lower ejection fractions and a higher prevalence of congestive heart failure than those without these abnormalities. The presence of LBBB and IVCD was associated with an \( \approx 1.5 \)-fold-increased risk of cardiac arrest and total mortality. RBBB either alone or in association with left-axis deviation failed to predict arrhythmic death or all-cause mortality.

**Comparison With Prior Studies**

The CASS registry evaluated the prognostic significance of BBB associated with coronary artery disease.\textsuperscript{4} In this registry, multivariable analysis established LBBB but not RBBB as a significant predictor of mortality independently of the degree of left ventricular dysfunction or coronary artery disease. Our results are consistent with the findings of the CASS registry.

LBBB is often associated with underlying hypertensive or ischemic heart disease.\textsuperscript{11} The association between conduction disease and structural heart disease has not been consistently demonstrated for RBBB.\textsuperscript{12} Intracardiac mapping studies have shown that the width of the QRS complex correlates with the degree of left ventricular myocardial abnormalities and disruption of His-Purkinje conduction.\textsuperscript{13,14} It is likely that ECG evidence of LBBB or IVCD, particularly in association with left anterior fascicular block, identifies patients with more disordered cardiac substrate and increased risk of progressive pump failure. The difference in association between primarily arrhythmic death with LVH and both forms of mortality with IVCD or LBBB may be related to varying degrees of myocardial disruption. It is possible that LVH may be an earlier form of the pathology that in more advanced stages results in conduction disease (IVCD or LBBB). The more advanced stage of myocardial disease identified by the presence of conduction disturbance may render it equally subject to both progressive pump failure and arrhythmia.

**Study Limitations**

Only 1 ECG was examined for each patient. This ECG was recorded at entry into the trial. Because the average duration of follow-up in the study was 39 to 41 months (for randomized and registry patients, respectively), it is possible that repeated ECGs during the course of the study (as is routinely done in clinical practice) might improve the utility of the ECG abnormalities to predict patients at risk for events. The ECG is insensitive for the detection of LVH. It seems likely that a technique such as echocardiography would result in improved correlations between the presence of LVH and events.

**Implications of Findings**

The indications for ICD placement in patients with coronary artery disease and depressed left ventricular function are rapidly increasing. A recent study has found that ICDs significantly reduce mortality in patients with coronary artery disease and severe left ventricular dysfunction (ejection fraction \( \leq 30\% \)).\textsuperscript{3} This finding was particularly significant in patients with QRS prolongation >120 ms.\textsuperscript{5} The overwhelming number of potential candidates for ICDs necessitates the identification of additional markers to more specifically define patients at high risk for mortality, particularly arrhythmic mortality, which can be prevented by ICD implantation. Our analysis demonstrated that ECG evidence of IVCD and LBBB was a marker of increased risk for total mortality, independent of the results of electrophysiology testing. Specifically, QRS prolongation in the form of LBBB but not RBBB was a high-risk marker for mortality. LVH was the single ECG predictor that selectively identified a risk for arrhythmic mortality independent of total mortality. Prospective studies are necessary to determine whether ECG evidence of LVH can be used in combination with other risk markers to select patients most likely to benefit from ICD implantation.

**References**

2. Almendral J, Villacastin J, Arenal A, Tercedore L, Merino J, Delcan J. Evidence favoring the hypothesis that ventricular arrhythmias have prognostic significance in left ventricular hypertrophy secondary to systemic hypertension. \textit{Am J Cardiol}. 1995;76:60D–63D.
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